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ORIGINAL ARTICLE

Cost-effectiveness of a tetravalent human papillomavirus vaccine in Germany

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Abstract
Aim Clinical trials have demonstrated the efficacy of the tetravalent human papillomavirus (HPV) vaccination in the prevention of cervical cancer and genital warts associated with HPV types 6, 11, 16 and 18. We used an empirically calibrated Markov cohort model of the natural history of HPV to assess the cost-effectiveness of the vaccine administered to 12-year-old girls alongside existing cervical screening programmes in Germany.
Subjects and methods The model estimated cervical cancer (CC), cervical intraepithelial neoplasia (CIN) and genital wart lifetime risks and total lifetime health care costs, life years gained and quality-adjusted life years (QALY) gained. The analysis was conducted from the perspective of the German health care payer.
Results In the base case (considering a lifetime duration of protection and 100% efficacy) it was estimated that 2,835 cervical cancer cases and 679 deaths could be prevented among a cohort of 400,000, at an incremental cost per QALY gained of 10,530 €. A total of 120 girls needed to be vaccinated to prevent 1 case of CC. Cost-effectiveness is sensitive to a duration of protection of less than 20 years and to the discount rate for costs and benefits.
Conclusion A policy of vaccinating adolescent girls has been recommended by the German Standing Committee on Vaccinations. This study has demonstrated that such a policy is cost-effective based on thresholds of cost-effectiveness that apply in Germany.

Keywords Human papillomavirus (HPV) vaccine · Cost-effectiveness · Germany

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Introduction

Cervical cancer is among the most common female cancers in many countries. In Germany, there are an estimated 6,190 new cases every year and about 1,660 deaths (Robert Koch-Institut 2008). Epidemiological research conducted during the last 15–20 years has provided overwhelming evidence for the aetiological role for infection with certain types of human papillomavirus (HPV) as the primary cause of cervical cancer. This virus is also responsible of other anogenital cancers (vulva, vaginal, anus, penile), head and neck cancers and genital warts (Munoz et al. 2006).

In Germany, cervical cancer is one of the target cancers covered by the statutory early detection cancer screening programme which was introduced in West Germany in 1971 and expanded to the eastern part of the country in 1991 (Schenck and von Karsa 2000). Women covered by statutory health insurance (over 90% of the population) are eligible to receive an annual cervical examination including

a Papanicolaou (Pap) smear beginning at the age of 20 years (Schenck and von Karsa 2000). Since the programme is based on opportunistic screening, the attendance rates have been low and only reached about 50% of females by the end of the 1990s (Schenck and von Karsa 2000). Therefore, screening alone cannot be expected to prevent all cases of cervical cancer.

The development of a prophylactic vaccine against HPV is a major breakthrough in the prevention of invasive cervical cancer. In 2006, the first prophylactic tetravalent HPV recombinant vaccine (HPV types 6,11,16,18) was granted marketing authorisation in the European Union. This tetravalent vaccine is indicated for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3) and external genital warts causally related to HPV types 6, 11, 16 and 18. In 2007, a bivalent vaccine (HPV types 16 and 18), indicated for the prevention of CIN grades 2 and 3 and cervical cancer causally related to HPV types 16 and 18, was approved for use by the European Medicines Agency. Both vaccines have been shown to be highly effective in large phase III clinical trials (FUTURE II Study Group 2007; Paavonen et al. 2007).

The objective of this study was to conduct a cost-effectiveness analysis of a tetravalent HPV recombinant vaccine in 12-year-old girls alongside the existing cervical cancer screening programme in Germany.

Study methodology

Model structure

A published and validated US Markov model of the natural history of HPV infection and cervical cancer (Myers et al. 2000) has recently been adapted to the UK (Kulasingam et al. 2008). We adapted this model to a German health care context to provide the basis of the cost-effectiveness analysis.

The Markov model follows a cohort of girls aged 12 up to age 85 through different health states covering HPV infection, cervical intraepithelial neoplasia (CIN), cervical cancer and genital warts. Movement between the health states is based on annual transition probabilities. Each year, an age-specific risk of acquiring an oncogenic HPV infection is applied to women in the cohort. Then, women infected with HPV can, with varying levels of probability, return to a 'well' state, suffer a persistent infection, progress to CIN 1, or in some cases, progress directly to CIN 2. Women who develop CIN 1, CIN 2 or CIN 3 are at risk of developing cervical cancer. The severity of cervical cancer is staged according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification system (FIGO I–IV). Each year women face an age-specific risk of dying from other causes.

Each year there is a risk of developing genital warts which varies depending on the woman's age. It is assumed that the genital warts will be cured within the year and the woman will return to a normal health state. Hence, the occurrence of genital warts is not associated with a disease state, but is rather considered as a transitory event in the model.

To be representative of the German health care context, the Markov model was adapted in three main ways. Firstly, the model was structurally adapted to reflect the screening and treatment pathways in Germany. In the USA and the majority of European countries, cytology screening results, using Pap smears, are classified according to the Bethesda system which reports LSIL (low-grade squamous intraepithelial lesion also known as CIN 1) and HSIL (high-grade squamous intraepithelial lesion also known as CIN 2/3). In Germany, the PAP (Munich II) system is employed (Schenck and Soost 1995). Therefore, the parameters in the model were adapted to correspond with the PAP system.

Secondly, the model was populated with German epidemiological and economic data derived from various sources that are detailed below. Thirdly, the model was calibrated to fit the age-specific cancer incidence curve for a screened population (Krebsregister 2003) and the results from a published decision-analytic model on the natural history of cervical cancer developed specifically for Germany (Siebert et al. 2006).

The model was programmed using the software TreeAge Pro (TreeAge Software Inc., Williamstown, MA, USA).

Vaccination strategy

We compared a routine vaccination programme of 12-year-old girls with a tetravalent HPV vaccine to the current cervical cancer screening programme. In the base case analysis it was assumed that vaccination coverage would be 80% of the eligible population and that screening practices would be unaffected by vaccination status.

Natural history parameters

Natural history parameters for progression and regression of disease used in the UK model were assumed to apply across Europe; hence, transition probabilities data were first extracted from the UK model (Kulasingam et al. 2008) (Table 1). Then, age-specific rates of HPV infection applied to the model were slightly modified to fit the age-specific cervical cancer incidence curve as part of the calibration process (Krebsregister 2003). The rates were higher for the age 20 and 21, which is consistent with the fact that

Table 1 Natural history parameters used in the model

Parameter	Age	Transition probability	Time period	Source
Normal				
Normal to HPV-infected state	14–18	0.020–0.080	12 months	Calibrated from Canfell et al. (2004)
	19–29	0.160–0.250		
	30–39	0.025–0.045		
	50+	0.0095		
HPV infection				
HPV infection to CIN 1 or CIN 2	All	0.0959	12 months	Canfell et al. (2004)
Proportion of HSIL that are CIN 2	All	0.1350	–	
CIN				
CIN 1 to well	12–24	0.7000	18 months	Calibrated from Canfell et al. (2004)
	25–39	0.5000		and Myers et al. (2000)
	40–49	0.2700		
	50+	0.1000		
CIN 1 to CIN 2	16–34	0.0297	12 months	Canfell et al. (2004)
	35+	0.1485		
CIN 1 to CIN 3	All	0.0301	12 months	
CIN 1 to HPV-infected state	16–34	0.2248	12 months	
	35+	0.1124		
Proportion CIN 1 regressing directly to well	All	0.90	–	
CIN 2 to CIN 3	16–34	0.0389	12 months	
	35–44	0.0797		
	45+	0.1062		
CIN 2 to CIN 1	All	0.2430	12 months	
CIN 2 to well or HPV-infected state	All	0.1901	12 months	
Proportion CIN 2 regressing directly to well	All	0.90	–	
CIN 3 to CIN 1	All	0.0000	12 months	
CIN 3 to CIN 2	All	0.0135	12 months	
CIN 3 to well or HPV-infected state	16–44	0.0135	12 months	
	45+	0.0100		
Proportion CIN 3 regressing directly to well	All	0.50	–	
CIN 3 to invasive cervical cancer	All	0.013	12 months	Canfell et al. (2004)
Cervical cancer				
Progression rates				
FIGO stage I		0.90	48 months	Myers et al. (2000)
FIGO stage II		0.90	36 months	
FIGO stage III		0.90	15 months	
FIGO stage IV		0.90	12 months	
Probability of symptoms				
FIGO stage I		0.11	12 months	Calibrated from Canfell et al. (2004)
FIGO stage II		0.23		and Myers et al. (2000)
FIGO stage III		0.60		
FIGO stage IV		0.80		

acquisition of HPV occurs very quickly after the onset of sexual activity. In addition, using the same approach as others (Siebert et al. 2006), we varied probability of symptoms for FIGO stages to obtain a distribution of cervical cancer stages similar to that of an unscreened population.

Five-year survival by cancer stage inputs were derived from Siebert et al. (2004). Age-specific hysterectomy proportions in the German general population (Siebert et al. 2004) and age-specific incidence of genital warts in women were additional inputs in the model (Hillemanns et al. 2008). The mortality rate of women in the general population comes

from official statistics (Federal Statistical Office Germany Statistics 2004).

German screening programme

In Germany, cervical screening is recommended from age 20 (Schenck and von Karsa 2000), with a follow-up of a repeat screen each year if the Pap result is normal (Siebert et al. 2006; Anttila and Jordan 2004; Bollmann et al. 2005). The model was structurally adapted to reflect the current screening pathways in Germany in the case of abnormal results, although substantial differences exist among general physicians in terms of management (Sheriff et al. 2007).

In the model, women presenting with LSIL (PAP III D) were assumed to undergo a repeat Pap smear every 3 months for 1 year, with colposcopy and biopsy if the lesion remains persistent, while those with HSIL (PAP IV) were assumed to undergo repeat cytology, colposcopy and biopsy with immediate effect (Siebert et al. 2006; Bollmann et al. 2005). Women who present with an atypical squamous cell of undetermined significance (ASC-US) result undergo a repeat Pap smear within 6 months, with colposcopy and biopsy if the lesion remains persistent (Siebert et al. 2006; Anttila and Jordan 2004; Bollmann et al. 2005).

The screening coverage rate was age specific, ranging from 17.7% for the age group 65–69 years up to 52.6% for the age group 45–54 years (European Commission 2002). Characteristics of the screening tests are presented in Table 2. Treatment of CIN was assumed to be 100% effective, resulting in the patient returning to a HPV-infected state without CIN; 90% of women with CIN 1 and all women with CIN 2/3 were assumed to be treated.

Vaccine efficacy

Based on recently published randomised clinical trials (Garland et al. 2007; Lacey 2008; FUTURE II Study Group 2007), the vaccine was assumed to be 100% effective against HPV types 6, 11, 16 and 18. In the model, it was estimated that these four types are responsible for 35% of CIN 1 cases. In addition, 55% of CIN 2/3 cases and 70% of cancer cases are caused by HPV types 16 and 18, and 90% of cases of genital warts are caused by HPV types 6 and 11 (Clifford et al. 2003, 2005; von Krogh 2001).

A high sustained efficacy against HPV 16/18-related CIN 2/3 has been demonstrated for the tetravalent vaccine in large phase II/III trials with follow-up periods (after start of vaccination) up to 5 years in phase II and up to 4 years in phase III (Lacey 2008). Moreover, a three-dose regimen of the tetravalent HPV vaccine induced high efficacy and stable anti-HPV levels for at least 5 years in a recent study, suggesting that the efficacy of this vaccine will be long lasting (Olsson et al. 2007). Therefore, the base case assumption was that duration of protection would be lifelong without the need for a booster, similar to the approach adopted in other cost-effectiveness analyses (Brisson et al. 2007b; Bergeron et al. 2008; Dasbach et al. 2008; Chesson et al. 2008).

Cross-protection effect of the vaccine was not considered in our analysis, although recent clinical cross-protection efficacy has been demonstrated against ten additional oncogenic human papillomavirus types (Brown 2007).

Costs

Unit costs are presented in Table 3. The analysis has been carried out from the German health care payer perspective. Medical resource use associated with screening and subsequent disease management, 5-year costs for treating cervical cancer by FIGO stage as well as costs for treatment of genital warts were derived from three German studies (Petry et al. 2008; Siebert et al. 2004; Hillemanns et al. 2008).

The cost of one 0.5-ml dose of a tetravalent HPV vaccine used in the model is 143.8 € and as three doses are required for effective disease prophylaxis the total cost per person vaccinated is 439.8 €. The unit cost of administration by a general practitioner (GP) is estimated to be 6.5 € per vaccination representing the mean fee for a GP visit for single vaccination administration across German federal states and insurance providers.

Utilities and discount rates

Utility estimates, used to calculate quality-adjusted life years (QALYs), are presented in Table 4. In the absence of European-specific data, these estimates were derived from a US time trade-off study conducted in 150 healthy female

Table 2 Sensitivity and specificity of Pap test, colposcopy and biopsy

	Value	Source
Sensitivity of a Pap test for detecting CIN 1/2	0.435	Petry et al. (2003)
Sensitivity of a Pap test for detecting CIN 3/cervical cancer	0.64	Karnon et al. (2004)
Specificity of a Pap test	0.95	Siebert et al. (2006)
Sensitivity of colposcopy with biopsy	0.9	Canfell et al. (2004) and Mitchell et al. (1998)
Specificity of colposcopy with biopsy	1	Karnon et al. (2004)

Table 3 Costs of detecting and treating precancerous lesions and cervical cancer

Parameter	Cost (€)	Source
Pap smear	24.8	a
Colposcopy	23.6	
Biopsy	106	
Treatment of CIN 1/CIN 2	336	Based on Petry et al. (2008)[b]
Treatment of CIN 3	1,498	
Treatment of FIGO I	7,523	Siebert et al. (2004)
Treatment of FIGO II	12,983	
Treatment of FIGO III	18,315	
Treatment of FIGO IV	17,152	
Treatment of genital wart	550	Hillemanns et al. (2008)

[a] Outpatient costs come from *Kassenärztliche Bundesvereinigung: Einheitlicher Bewertungsmaßstab für ärztliche Leistungen*. http://www.kbv.de/ebm2000plus/EBMGesamt.htm. Accessed 22 Nov 2006

[b] This represents the mean cost of interventional procedures in Petry et al. (2008), assuming that PAP III and PAP III B were CIN 1 or CIN 2 and that PAP IV were CIN 3

volunteers (Myers et al. 2004). The expected time considered in each state of health was the same as that in a UK analysis using the same core model (Kulasingam et al. 2008). The utility for those surviving cervical cancer was assumed to be 1.0.

In the absence of specific recommended discount rates for prevention technologies, the base case rates applied were those recommended in Dutch pharmacoeconomic guidelines (Dutch Health Care Insurance Board 2005). Discount rates of 4% for costs and 1.5% per annum for future health benefits (LYGs and QALYs) were applied in the base case. Given the high uncertainty in the appropriate discount rate a range from 0 to 5% for costs and benefits was also applied in sensitivity analysis.

Outputs and analyses

The model was used to produce estimates of cervical cancer, CIN and genital wart lifetime risks, total lifetime costs and incremental cost-effectiveness ratios (ICERs): the incremental cost per life year gained (LYG), and incremental cost per QALY gained.

The number needed to vaccinate (NNV) to prevent cases of cervical cancer is a useful measure of vaccine effectiveness (Brisson et al. 2007a). Using the natural history model, the NNV with the tetravalent HPV vaccine in Germany was estimated. NNV was defined as the number of 12-year-old girls that are needed to be vaccinated to prevent an HPV-related event during their lifetime, calculated as follows: NNV = 1/ARR, with ARR representing attributable risk reduction (Brisson et al. 2007a).

One-way sensitivity analysis was undertaken to explore the impact on cost-effectiveness of varying a range of key parameters for duration of vaccine protection, vaccine and administration costs, Pap sensitivity, utilities, discount rates and screening coverage. The impact on cost-effectiveness of a scenario of administering a booster vaccine (one dose) to 50% of females originally vaccinated was also explored.

Results

Model validation

The model was calibrated to predict a lifetime risk of cervical cancer of 3.1% and a lifetime risk of death due to cervical cancer of 1.08% in Germany in the absence of screening. Moreover the model predicts the following distribution for FIGO stage at diagnosis (before screening implementation): FIGO I: 38.4%, FIGO II: 30.3%, FIGO III–IV: 31.3%. These predictions are consistent with findings from Siebert et al. (2006).

As shown in Fig. 1, the model was also calibrated so that the predicted age-specific annual incidence of invasive cervical cancer in the German screened population was similar to the observed data for Germany (Krebsregister 2003), demonstrating the validity of the model adaptations for the German context.

Table 4 Utility values used in the model

Health status	Utility value	Time period
Routine screening Pap smear	0.98	1 month
ASC-US diagnosis from Pap smear	0.94	2 months
LSIL/HSIL diagnosis from Pap smear	0.91	2 months
Genital warts	0.91	85 days
CIN 1	0.91	2 months with 10 months follow-up
CIN 2/3	0.87	2 months
FIGO I	0.76	5 years
FIGO II–IV	0.67	5 years

Source: Myers et al. (2004) and Kulasingam et al. (2008)

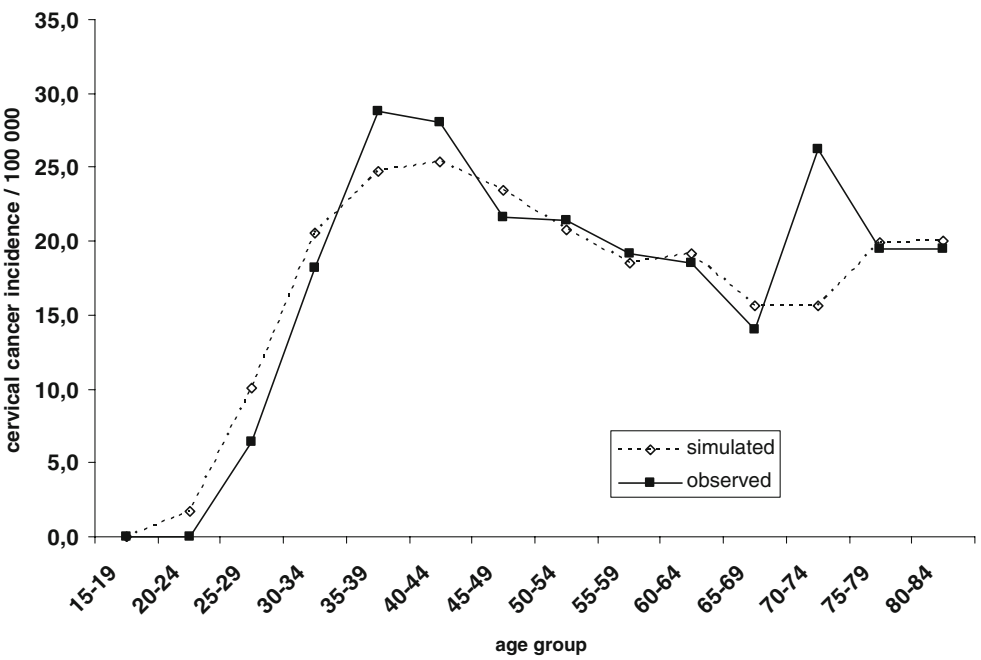

Fig. 1 Simulated and observed cervical cancer incidence for the screened population

Health benefits

Under base case assumptions (vaccination coverage rate of 80% and lifelong duration of protection) for a birth cohort of about 400,000 females in Germany, the model estimates that 2,835 cervical cancer cases and 679 deaths could be avoided. In addition, 7,776, 5,921 and 9,962 cases of detected CIN 1, 2 and 3 cases, respectively, and 28,310 cases of genital warts could be avoided (Table 5).

Base case cost-effectiveness analysis

The incremental cost-effectiveness of a screening plus vaccination programme from a health care payer perspective in Germany versus screening alone was estimated to be 15,684 € per LYG and 10,530 € per QALY gained (Table 6). These ratios are well below the incremental cost-effectiveness threshold relevant to Germany of 50,000 € per QALY. Therefore, a vaccination programme with a tetravalent HPV vaccine alongside the current screening programme can be considered as a cost-effective strategy.

The cost per cervical cancer avoided (undiscounted) is estimated at 24,519 € and the cost per event avoided (cervical cancer, CIN or female genital warts) at 1,253 €.

Sensitivity analyses

The base case assumes lifetime duration of protection for vaccination. Incremental cost-effectiveness was sensitive to durations of protection of less than 20 years, but not for longer durations up to lifetime. Furthermore, a scenario in which booster vaccination is provided (after 10 years) for 50% of females originally vaccinated in order to ensure lifetime protection produced an increased cost-effectiveness ratio compared to the base case, primarily due to the impact of the increased cost of providing a booster (Table 7).

Cost-effectiveness was very sensitive to the discount rate used, with higher joint discount rates for costs and benefits resulting in higher cost-effectiveness ratios (Table 7). If costs and health benefits were jointly discounted at 3%, which is similar to the rate recommended in several economic evaluation guidelines across Europe, the incre-

Table 5 Estimated number of cases avoided per 400,000 cohort[a]

Strategy	Cervical cancer	Deaths from cervical cancer	CIN 3 detected	CIN 2 detected	CIN 1 detected	Genital warts
Screening only	4,783	1,146	21,514	12,868	23,455	40,299
Screening and vaccination	1,948	468	11,552	6,947	15,679	11,989
Cases avoided	2,835	679	9,962	5,921	7,776	28,310

[a] Assuming 80% coverage rate, lifetime duration of protection

Table 6 Incremental cost-effectiveness from a German health care payer perspective

	Costs (€)	Mean LYGs	Incremental cost/LYG (€)	QALYs	Incremental cost/QALY (€)
Screening only	314.1	42.55	–	42.4989	–
Screening + vaccination	612.2	42.569	15,684	42.5272	10,530

mental cost-effectiveness increased to 18,636 € per QALY gained. If the discount rate is 5% for both costs and benefits, the ICER increased to 42,493 € per QALY gained. In contrast, with zero discounting of costs and benefits the ICER was less than 3,049 € per QALY gained.

The cost-effectiveness ratio was insensitive to changes in treatment costs, efficacy, utility parameters and application of a zero disutility for a routine Pap smear test (Table 7). Varying the sensitivity of the Pap smear for detection of CIN 1/2 or CIN 3 had a small impact on the cost-effectiveness ratio.

The impact of different screening strategies associated or not with vaccination was also considered. In our base case analysis, 2,835 incremental cases of cervical cancer and 679 incremental deaths could be avoided thanks to the introduction of the HPV vaccination compared to the current screening programme alone. If the screening coverage rate was increased by 20% without HPV vaccination, only 717 incremental cases of cervical cancer and 231 incremental deaths from cervical cancer could be avoided. If the screening coverage rate decreased by 20% after the vaccination programme implementation, 2,442 additional cancer cases and 541 additional deaths could be avoided. In this context, introducing HPV vaccination in association with a screening programme (less or as efficient as the current one) appeared to be more efficient than only improving the existing screening intervention.

Number needed to vaccinate

The NNV to prevent one case of cervical cancer was estimated to be 120 based on a birth cohort of 400,000 12-year-old girls. For this we assumed a vaccination coverage rate of 100%. For CIN 1, CIN 2 and CIN 3 related to HPV the NNV to prevent one case was estimated by the model to be 45, 55 and 33, respectively, and the NNV for genital wart was estimated to be 11. Six girls need to be vaccinated to prevent one HPV-related clinical event.

Table 7 Sensitivity analysis for key parameters

	Incremental cost/LYG (€)	Incremental cost/QALY (€)
Base case	15,684	10,530
Duration of protection		
Lifelong achieved with a booster[a]	24,943	17,034
20 years	28,991	19,445
Vaccine efficacy		
90% efficacy	16,872	11,681
Vaccine cost		
-20%	12,053	8,092
20%	19,321	12,972
Treatment cost (CIN and cancer)		
-20%	16,311	10,951
20%	15,063	10,113
Pap sensitivity for detection of CIN 1		
50%	16,394	10,731
Pap sensitivity for detection of CIN 2/3		
55%	11,400	8,211
75%	23,069	12,972
Utilities		
-50% duration	NA	11,037
+50% duration	NA	9,313
Discount rate for costs/benefits		
0%/0%	4,138	3,049
3%/3%	30,258	18,636
5%/5%	81,632	42,493
5%/0%	7,386	5,442
Exclusion of genital warts	16,689	11,658

[a] One dose of booster given 10 years after the three doses in 50% of the cohort. No efficacy is assumed after 10 years for the 50% of non-vaccinated girls

Discussion

Although previous studies have assessed the cost-effectiveness of HPV vaccination in other European countries (Bergeron et al. 2008; Dasbach et al. 2008), this is the first analysis conducted on HPV vaccination Germany. Until now, cost-effectiveness studies specific to Germany have focussed on the cost-effectiveness of several screening strategies (Mittendorf et al. 2003; Siebert et al. 2004; Sheriff et al. 2007). Based on a vaccination coverage rate of 80%, the use of a quadrivalent vaccine alongside the current national cervical cancer screening programme was found to be a cost-effective public health initiative compared to screening alone, with an incremental cost per QALY gained and LYG gained that was well within the accepted threshold for cost-effectiveness in Germany (Siebert et al. 2004). In terms of health benefits the model has shown that the introduction of a tetravalent vaccine has the potential to substantially reduce the public health burden associated with cervical cancer, with an estimated reduction of nearly 3,000 cases and 700 deaths for a cohort of 400,000 females vaccinated at the age of 12. Sensitivity analysis has shown that the results are relatively insensitive to varying the base case parameters for screening and vaccine coverage rates, natural history, Pap smear sensitivity, cost and utility variables. The only variable that results in cost-effectiveness ratios above 50,000 € per QALY gained was if a very short duration of protection is assumed. An incremental cost per LYG above 50,000 € was associated with applying relatively high rates of discounting (5%) for both costs and health outcomes. There is much debate regarding the value of the discount rate used, particularly when evaluating public health programmes such as vaccination. Discounting may undervalue preventive interventions for which the benefits appear long after the costs have been paid, such as HPV vaccination programmes (Crott 2007).

We note some limitations in our analysis. Firstly, utility estimates, required to calculate cost per QALY, were derived from a study conducted in the USA (Myers et al. 2004). To our knowledge, no specific data for Germany, or any other European countries, have been published so far. In addition, our utility estimates are conservative compared with estimates used in other published cost-effectiveness analyses (Brisson et al. 2007b; Goldie et al. 2004). Secondly, we considered a compliance of 100% for the three doses of the vaccines. It may happen that some girls received only two doses instead of three, although it is difficult to make an assumption on this. Lastly, previous German economic studies suggested that HPV testing would improve screening performance (Sheriff et al. 2007). However, we decided not to include HPV testing in our analysis as HPV testing is not standard practice in Germany.

Our analysis can be considered as conservative in several aspects. Firstly, as we used a Markov model it was not possible to include the herd immunity effects of the vaccination programme. For instance, it is not possible to assess the indirect benefits of the vaccine by avoiding HPV-related diseases in males. To measure these additional benefits, a dynamic transmission model would be necessary. A number of dynamic models exist (Dasbach et al. 2006), among which two have examined the cost-effectiveness of quadrivalent HPV (6/11/16/18) vaccination strategies in Europe (Jit et al. 2008; Dasbach et al. 2008). Secondly, our model did not cover the cross-protection effect of the vaccine and the impact of the tetravalent HPV vaccine on the prevention of other cancers, in particular vaginal and vulval cancers or laryngeal papillomas, related to HPV types 6, 11, 16 and 18. A recent US cost-effectiveness analysis showed that the inclusion of potential additional benefits of preventing anal, vaginal, vulvar and oropharyngeal cancers could decrease the cost per QALY by at least 20% (Chesson et al. 2008). Furthermore, indirect costs of lost productivity were not included, which would potentially further improve cost-effectiveness from a societal perspective.

Economic analyses such as ours can help to provide information for public health policy and reimbursement decisions on an HPV vaccination programme. In the case of HPV vaccines, it can also highlight the difference between a bivalent and a quadrivalent vaccine. The types 6 and 11 included in the quadrivalent vaccine are responsible for 90% of genital warts and for around 10% of CIN 1. In our model, the cost-effectiveness ratio is increased by 10% when benefits of the vaccine on genital warts are removed. This result is modest as compared to findings from other countries which can be the results of not having an HPV type specific model. A Canadian cost-effectiveness study showed that the cost-effectiveness ratio of vaccinating a cohort of 12-year-old girls with the quadrivalent (HPV 6/11/16/18) and with the bivalent (HPV 16/18) vaccine would be of Canadian $20,512 and 31,060/QALY gained, respectively (Brisson et al. 2007b). Another study, conducted by the Centers for Disease Control and Prevention (CDC) in the USA estimated that vaccination of 12-year-old girls with the quadrivalent (HPV 6/11/16/18) vaccine had a cost-effectiveness ratio at least 30% lower than with the bivalent (HPV 16/18) vaccine (Chesson et al. 2008).

To date, there has been limited use of economic analyses for such decisions in Germany compared to some other European countries such as the UK. However, this might change with German insurance companies increasing their focus on cost and forthcoming requirements for economic analysis to be performed as part of the reviews of new interventions by the German Health Technology Agency, the Institute for Quality and Efficiency in Health Care, which advises the Federal Ministry of Health. In addition,

the German Standing Committee on Vaccinations (STIKO) at the Robert Koch Institute has recommended the introduction of universal vaccination against HPV types 16 and 18 for all girls between the age of 12 and 17 in order to reduce the incidence of cervical cancer in the population (Robert Koch Institute 2007). Our analysis focussed on a single cohort, but dynamic transmission models, which allow seeing the impact of catch-up programmes, conclude that an initial catch-up programme for girls aged up to 18 is likely to be cost-effective (Dasbach et al. 2008; Jit et al. 2008). The STIKO statement includes an assessment of the possible impact of an HPV vaccination programme in Germany. For a 1996 birth cohort and assuming a lifetime vaccination effectiveness rate of 92.5%, it was estimated that the NNV to prevent one case of cervical cancer was 98. These estimates are similar to the NNV of 120 estimated from our model for Germany.

A policy issue that needs addressing in Germany is the concern that the current policy of annual screening of >20-year-old females is sub-optimal. A recent German study demonstrated that cost-effectiveness could be improved with screening intervals of 3–5 years, concluding that the German cervical screening programme was in need of reform (Bischoff-Everding et al. 2006). The effectiveness of existing screening strategies could therefore constrain the cost-effectiveness of screening plus vaccination programmes for HPV infection.

A further policy issue is that there is a risk of lower adherence to cervical cancer screening with a universal vaccination programme, which could be addressed via education campaigns to advise young women of the continued importance of attending cervical screening.

In conclusion, our analysis supports a national programme of adding the HPV tetravalent vaccine in adolescent females to the national cervical screening programme in Germany as a cost-effective strategy from a health care and public health perspective, due to the significant impact it can have on reducing the burden of disease associated with HPV-related diseases.

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